Surgical Treatments for Chronic Subdural Hematomas: A Comprehensive Systematic Review

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Key words
- Chronic subdural hematoma
- Evidence-based medicine
- Operative surgical procedures
- Randomized controlled trials
- Surgical treatments for chronic subdural hematomas
- Systematic review

Abbreviations and Acronyms
CI: Confidence interval
CSDH: Chronic subdural hematoma
GCS: Glasgow Coma Scale
I^2: Inconsistency index
ITT: Intention-to-treat
mRS: Modified Rankin Scale
RCT: randomized controlled trial
RR: Risk ratio

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BACKGROUND: **Chronic subdural hematomas (CSDHs) are common neurosurgical conditions among elderly patients.**

OBJECTIVE: **To perform a detailed critical appraisal of all randomized controlled trials (RCTs) of surgical treatments for chronic subdural hematomas and to quantify their intervention effects.**

METHODS: **We performed a broad search for all RCTs with no language or date restrictions, asked the authors for missing data, and applied the Cochrane methods.**

RESULTS: **A total of 24 RCTs involved 1900 patients and 15 comparisons. All outcomes of practical interest were analyzed. Postoperative drainage after burr-hole evacuation reduced the rate of recurrence (risk ratio 0.48, 95% confidence interval 0.34—0.66, $P < 0.00001$) with no other clear benefits or complications.**

CONCLUSIONS: **This comprehensive, best evidence—based, quantitative, systematic review indicates that the use of a closed system drainage after burr-hole evacuation reduces the rate of recurrences but has no other significant differences. The findings also suggest that: (1) treatment with twist drills is equivalent to that with burr holes; (2) the postoperative bed header in the elevated position might reduce the length of hospital stay; (3) irrigation of the subdural space with thrombin solution in patients with high risk of recurrence might reduce this risk; and (4) treatment with twist drill followed by a closed system drainage during 48 hours, instead of 96 hours, might reduce general complication rates. Most of the trials suffered from unclear or high risks of bias and many involved small samples, precluding strong and definitive conclusions.**

INTRODUCTION

Chronic subdural hematomas (CSDHs) are among the most common neurosurgical conditions, and they affect mainly the aged patient,[1-11] with an incidence reaching 58.1 per 100,000 in the population that is 65 years old or older.[12] As the world population becomes progressively older,[13] the overall incidence is expected to increase. CSDHs occur bilaterally in approximately 19% of the cases and affect the male sex more often.[2,3,7,8,12,14-26]

The cleavage plane where subdural hematomas lie is the loose dural border cell layer located in the inner portion of the dura mater.[27] CSDHs result from bleeding from parasagittal bridging veins, caused by trauma of slight or moderate intensity.[28] The subdural hematoma becomes covered by a thin membrane in its inner aspect and a thick outer membrane that contains macrocapillaries (sinusoidal vessels) with increased permeability and endothelial gap junctions that permit the leakage of blood and enlargement of the hematoma.[29,30]

Subdural hematomas are classified into acute (within 3 days of trauma), subacute (4—20 days), and chronic (after 20 days), and cases with no history of trauma are classified according to the total duration of symptoms.[19] The diagnosis of CSDH is difficult to make on the basis of clinical findings alone[31] and requires the use of examinations such as computed tomography or magnetic resonance imaging. The overall surgical mortality has ranged from 0% to 32%[8,14,19,20,22,23,32] and the recurrence rate from 0.36% to 33.3%.[23,33]

Some authors have found that removal of the membranes is unnecessary to cure the disease,[25,34] whereas others have observed that the adequate drainage of hematoma decreases the vascularity and cellularity of the membranes, which eventually disappear.[35-38]

As a general rule, asymptomatic CSDHs are considered nonsurgical. In the same way, asymptomatic recollections of hematoma, detected by imaging methods and showing no signs of cerebral compression, are not subjected to new surgical drainage. The decision to operate or to reoperate is based on the presence of symptoms and clinical or imaging signs of cerebral compression.[39-44] The definition of recurrence used by most authors and adopted in this review is that of a

postoperative symptomatic recollection of hematoma that requires reoperation of any kind, including redrainage by percutaneous needle aspiration.

There are various techniques to open the skull to remove subdural hematomas. Twist-needle craniostomies are usually less than 2 mm in diameter.[45] Weigel et al.[46] classified openings of the skull up to a diameter of 5 mm as twist-drill craniostomy, openings of up to 30 mm as burr-hole craniostomy or enlarged burr-hole craniostomy, and larger openings as craniotomy. The sizes of the instruments available to create twist-drill and burr-hole craniostomies cross the 5-mm boundary. In an analysis of the results of 5 retrospective studies comparing the recurrence rates after 1 versus 2 burr-hole craniostomies, investigators found no significant differences.[47]

Many studies have reported on different types of interventions during the surgical treatment of CSDHs, but questions remain regarding their effectiveness and safety. The many doubts concerning the surgical treatment of CSDHs require a systematic review analyzing the evidences available.[48-50]

The objective of the present systematic review was to collect and analyze all of the randomized controlled trials (RCTs) available, to evaluate their risks of bias critically, and to quantify the effects of the various procedures for the surgical treatments of CSDHs by applying the Cochrane Collaboration methods and its statistical software.[51] This review addresses whether one type of treatment is more effective or safer than other types.

MATERIALS AND METHODS

We used the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions*.[51]

Types of Studies

We aimed at identifying and analyzing all of the RCTs currently available, comparing one type of intervention for the surgical treatment of CSDHS with another type of intervention or with nonsurgical treatment. One study based on minimization[52] was included because this method is considered equivalent to randomization.[51,53]

Types of Participants

Patients were included of any sex or age with CSDHs. Patients with CSDHs secondary to cranial procedures and those presenting with cerebrospinal fluid shunt, calcified hematomas, and other subdural collections, such as hygromas, effusions, and empyemas, were excluded.

Outcomes

All outcomes of practical value described in the included studies were analyzed, preferably at their final follow-ups.

Search Methods

Our search was not limited by language or date of publication. We searched the following electronic databases: MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, LILACS, IBECS (Spain), and the *meta*-Register of Controlled Trials. We also searched the reference lists of studies and books. The corresponding authors of the included studies were contacted for unpublished or unclear data. The study selection and data extraction were performed by 2 authors independently, and there were no disagreements. Analyses of the study data were performed by all of the authors independently, followed by discussions.

Assessment of Risk of Bias

Biases are systematic errors or deviations from the truth that can cause underestimation or overestimation of the intervention effects. The assessment of the risks of bias provides an estimate of the extent to which the results of a trial can be trusted. We applied the Cochrane Collaboration domain-based risk of bias tool, which classifies the risks as low, high, or unclear.

Measurements of Treatment Effect

Statistical analyses for the measurement of the treatment effects were performed with the Cochrane Review Manager software (RevMan), version 5.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). For dichotomous outcomes, we used risk ratios (RR) with 95% confidence intervals (CIs), measurements that are preferable to odds ratios.[51] For continuous outcomes, mean differences between the effects of the interventions were used with 95% CIs. *P* values also were recorded. Meta-analyses were performed for 2 or more comparable studies of interventions delivered in similar manners. Statistical heterogeneity among studies was evaluated by the overlapping of CIs in forest plots, by the χ^2 test, and by the inconsistency index. Fixed-effect estimates of the Mantel-Haenszel method were used. When heterogeneity was substantial, with an inconsistency index greater than 50%, the random-effects model was applied. When the losses to follow-up made an intention-to-treat analysis impossible, we performed available cases analyses.

RESULTS

The total number of citations found in our searches of databases, reference lists, and books was 1739, and 1715 of them were excluded. The 24 remaining studies met our inclusion criteria, with data available for 1900 patients, mostly adults (Table 1). We found no RCT dedicated specifically to children. Corresponding authors supplied unpublished data regarding 9 RCTs. The studies were performed in various regions of the world. Nineteen studies were analyzed as intention to treat. Analyses were limited to available cases in 6 studies because of attrition. Sensitivity analyses were performed when necessary.

Risk of Bias in Included Studies

The assessments of the risk of bias in the included studies are summarized in Table 2.

Random Sequence Generation (Selection Bias). There was low risk of bias in 11 studies, unclear risk in 9 studies, and high risk in 4 studies. These 4 studies[61,64,66,76] used alternation as the method for random sequence generation (Tables 1 and 2).

Allocation Concealment (Selection Bias). Only 6 studies presented adequate allocation concealment,[55,69-72,75] whereas 12 presented unclear risk of bias and 6 presented high risk of bias. Among these 6 high-risk studies, 4 used alternation,[61,64,66,76] and 2 had the random allocation sequence open to the staff[59,74] (Tables 1 and 2).

Blinding of Personnel and Participants (Performance Bias). Twenty two trials presented a high risk of performance bias (Table 2) because blinding of personnel and participants (patients) are very

Table 1. Included Studies

First Author and Year	Country	Age Range in Years (Mean or Means)*	Number of Randomized Patients, N	Method of Random Sequence Generation (Selection Bias)	Method of Allocation Concealment (Selection Bias)	ITT or ACA
Abouzari 2007[54]	Iran	21–88 (mean 56.5)	84	Unstated	Unstated	ITT
Ahmed 2011[55,†]	India	17–85 (mean 53)	51	Computer software	Sequence concealed	ITT
Erol 2005[56]	Turkey	20 or older, except for one	70	Unstated	Unstated	ITT
Gai 2002[57]	China	8–83 (mean 62.5)	120	Unstated	Unstated	ITT
Gjerris 1974[58]	Denmark	33–80	9	Random numbers tables	Unstated	ITT
Gokmen 2008[59,†]	Turkey	35–98 (mean 67)	70	Random numbers table	Allocation sequence open to the staff	ITT
Gurelik 2007[60]	Turkey	Age range unstated (means 58.4 and 59.2)	80	Unstated	Unstated	ITT
Hirashima 2002[61]	Japan	47–79 (means 65.7 and 66.7)	48	Alternation		ACA
Ishfaq 2009[62]	Pakistan	30–97 (mean 60)	60	Random numbers table	Unstated	ITT
Javadi 2011[63,†]	Iran	18–96 (mean 67)	40	Unstated	Unclear bias risk‡	ITT
Kaliaperumal 2012[64,†]	Ireland	17–91	52	Alternation		ACA
Laumer 1989[65]	Germany	Adults	144	Unstated	Unstated	ITT
Muzii 2005[66]	Italy	63–94 (means 78.7 and 76.3)	61	Alternation		ACA
Nakaguchi 2000[67]	Japan	41–92 (mean 68.1)	63	Unstated	Unstated	ITT
Nakajima 2002[68]	Japan	47–93 (mean 72.8)	46	Unstated	Unstated	ITT
Poulsen 2014[69,†]	Denmark	Minimum 18 (mean 67.5)	50	Computer software	Sealed envelopes	ACA
Ram 1993[52,†]	Israel	Adults (means 71.5 and 70.4)	37	Minimization with no random component		ITT
Santarius 2009[70]	UK	36–95 (mean 76.8)	215	Web-based block randomization	Sealed envelopes	ITT and ACA
Shimamura 2009[71,†]	Japan	Minimum 18 (means 70.5 and 74.1)	79	Coin toss		ITT
Sindou 2010 and Ibrahim 2010[72,†]	France	36–92 (mean 75)	65	Papers mentioning either 48 h or 96 h, similar in shape, extracted by resident a few hours before surgery		ITT
Singh 2011[73]	India	No infants (means 59.8 and 61.2)	100	Computer software	Unreported	ACA
Singh 2014[74,†]	India	9–95 (one patient younger than 18 in each group)	200	Computer software	Allocation sequence open to the staff	ITT
Tsutsumi 1997[75]	Japan	19–92 (mean 67)	118	Coin toss		ITT
Wakai 1990[76]	Japan	42–84 (means 70.8 and 71.7)	38	Alternation		ITT
Total			1900			19 ITT and 6 ACA

Sindou 2010[72] and Ibrahim 2010[77] refer to the same study.
ITT, intention-to-treat analyses; ACA, available cases analyses.
*Age range: mean age of all patients or age means of each randomized group.
†Authors supplied unpublished data to clear doubts about their studies.
‡In the study by Javadi et al., allocation sequence was only available to the first author, and after installing the burr-hole and irrigation, the staff was informed regarding whether to insert the drainage system or to terminate surgery.

difficult or impossible to be undertaken in most types of interventions used in surgical treatments. Only 2 studies presented a low risk of bias, one that tested the postoperative use of a drug[69] and the other the use of thrombin irrigation during surgery[71]; both interventions were compared with placebos with adequate blinding of the personnel and participants.

Blinding of Outcome Assessors (Detection Bias). Low risk of detection bias was found in 4 studies,[63,69,71,72] in which outcome assessments were performed by blinded physicians. High risk of bias was

Table 2. Risk of Bias Summary for Each Study

Seven Domains at Right, according to the Cochrane Collaboration methods[51] (24 Studies Evaluated)	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection bias)	Blinding of Participants and Personnel (Patients and Staff) (Performance Bias)	Blinding of Outcome Assessment (Detection Bias)	Incomplete Outcome Data (Attrition Bias). Details in Table 3	Selective Reporting (Reporting Bias)	Unevenness of Preoperative mRS (Other Bias). Details in Table 4
Abouzari 2007[54]	?	?	H	?	L	?	
Ahmed 2011[55]	L	L	H	H	L	L	
Erol 2005[56]	?	?	H	?	L	?	
Gai 2002[57]	?	?	H	?	L	?	
Gjerris 1974[58]	L	?	H	H	L	?	
Gokmen 2008[59]	L	H	H	H	L	?	
Gurelik 2007[60]	?	?	H	?	L	?	
Hirashima 2002[61]	H	H	H	H	H	?	
Ishfaq 2009[62]	L	?	H	?	L	?	
Javadi 2011[63]	?	?	H	L	L	?	
Kaliaperumal 2012[64]	H	H	H	H	H	L	?
Laumer 1989[65]	?	?	H	H	L	?	
Muzii 2005[66]	H	H	H	?	H	?	
Nakaguchi 2000[67]	?	?	H	H	L	?	
Nakajima 2002[68]	?	?	H	?	L	?	
Poulsen 2014[69]	L	L	L	L	H	L	
Ram 1993[52]	?	?	H	H	L	?	
Santarius 2009[70]	L	L	H	?	L/H	L	?
Shimamura 2009[71]	L	L	L	L	L	?	
Sindou 2010 and Ibrahim 2010[72]	L	L	H	L	L	?	
Singh 2011[73]	L	?	H	?	H	?	
Singh 2014[74]	L	H	H	H	L	?	
Tsutsumi 1997[75]	L	L	H	?	L	?	
Wakai 1990[76]	H	H	H	?	L	?	
Total	11 L 9 ? 4 H	6 L 12 ? 6 H	2 L 0 ? 22 H	4 L 11 ? 9 H	19 L 0 ? 6 H	4 L 20 ? 0 H	0 L 2? 0 H

?, unclear risk of bias; H, high risk of bias; L, low risk of bias.

detected in 9 studies, in which outcome assessments were performed by unblinded assessors. Unclear risk was found in 11 studies, in which blinding of outcome assessments was unreported or the clinicians were masked to outcome assessments only when possible (Table 2).

Incomplete Outcome Data (Attrition Bias). Attrition was present in 5 studies,[61,64,66,69,73] and in another study[70] for outcomes other than recurrence only (Tables 2 and 3). The remaining 19 studies did not present losses to follow-up.

Selective Reporting (Reporting Bias). The research protocols of 4 studies[55,64,69,70] were obtained, and the differences found were not causes of selective reporting, indicating a low risk of bias. In the remaining 20 studies, although no selective reporting was identified comparing the results with the methods sections of the articles, the research protocols were not obtained and were classified as presenting an unclear risk of bias (Table 2).

Unevenness of Preoperative Modified Rankin Scale (mRS) Scores (Other Bias). The mRS is a reliable instrument to measure global disability, originally applied for evaluating stroke patient outcomes and as end point in RCTs.[78] The unevenness of preoperative

Table 3. Details of the Risks of Attrition Bias: Incomplete Outcome Data

Low risk	Abouzari 2007,[54] Ahmed 2011,[55] Erol 2005,[56] Gai 2002,[57] Gjerris 1974,[58] Gokmen 2008,[59] Gurelik 2007,[60] Ishifaq 2009,[62] Javadi 2011,[63] Laumer 1989,[65] Nakaguchi 2000,[67] Nakajima 2002,[68] Ram 1993,[52] Santarius 2009[70] (for recurrences), Shimamura 2009,[71] Sindou 2010 & Ibrahim 2010,[72] Singh 2014,[74] Tsutsumi 1997,[75] Wakai 1990.[76]	No attrition reported except for Nakajima 2002,[68] in which one case was missing from one group (supine), for an observed event rate of 4/34 for this group (supine) and 3/21 for the other group (sitting). A sensitivity analysis, considering the missing case as having recurrence or no recurrence, showed that the direction of the results and the conclusion of statistical nonsignificance did not change. Santarius et al.[70] stated on page 1070 of the trial report that their primary outcome (recurrence) was measured for all patients.
High risk	Hirashima 2002[61]	Nine of the 24 patients assigned to the etizolam group were dropped from the study because the duration of drug administration was less than 3 days. In the reevaluation, performed between 2 and 3 months postoperatively, 3 more patients from the etizolam group were lost to follow-up, and no data were available concerning their outcomes. There were no losses in the control group.
	Kaliaperumal 2012[64]	Two patients, one from each group, were excluded from the trial because of premature dislodgment of the drain before 48 hours. The event rates for dichotomic outcomes were 0/25 and 1/25.
	Muzii 2005[66]	Fifteen patients were lost to or had incomplete follow-up and were excluded from the study, and the data available are on the remaining 46. The event rates ranged between 0/22 and 5/24.
	Poulsen 2014[69]	Among the 50 randomized patients, 3 were excluded because they withdrew their consents after randomization, one from the perindopril arm and 2 from the placebo arm; no other information was available about them. The event numbers for dichotomic outcomes were 0 and 2.
	Santarius 2009[70] (for outcomes other than recurrence)	Losses were reported for their secondary outcomes. The losses for the evaluation of Glasgow Coma Scale at discharge were 14/108 (13%) in the drain group and 10/107 (9.4%) in the no-drain group. At 6 months, a follow-up questionnaire was mailed to patients for them to complete, with assistance from family members or caregivers if necessary, asking about their accommodation, independence, mobility status, and modified Rankin Scale scores. The incomplete responses to these postal questionnaires for secondary outcomes were high: (a) 31/108 (28.7%) in the drain group; (b) 20/107 (18.7%) in the no-drain group; and (c) 51/215 (23.7%) among all of the randomized patients. The observed event risk for these clinical outcomes ranged between 5/67 (7.5%) and 64/76 (84%) in the drain group and between 9/67 (13%) and 60/85 (71%) in the no-drain group. Because of the losses, analyses of the secondary outcomes were performed based on the available cases. An unusual feature of this study, compared with the other reviewed trials, was that it did not report a final (6 months) follow-up *clinical* examination in *all* patients, for their primary and secondary outcomes.
	Singh 2011[73]	Three patients from the same group were lost to follow-up. The event rates for recurrences and mortality ranged between 0 and 4.

mRS scores in 2 trials[64,70] is discussed in Table 4.

Effects of Interventions

The comparisons and outcomes presented in this review are those contained in the primary studies. The 24 RCTs included 15 comparisons of practical interest. We performed the statistical analyses using the Cochrane Collaboration software on the raw numerical data extracted from the studies. Only the main comparisons and effects are presented here. Details on the effects of all of the interventions, with their values and comments, are shown in Table 5.

Comparison 1. Treatment of CSDH with burr hole and irrigation of the subdural space associated with (A) a postoperative closed drainage system to a soft bag versus (B) no postoperative drainage. This comparison was performed in 8 studies involving 828 patients: Ahmed et al.,[55] Erol et al.,[56] Javadi et al.,[63] Laumer et al.,[65] Santarius et al.,[70] Singh et al.,[74] Tsutsumi et al.,[75] and Wakai et al.[76] A meta-analysis combining the data from the 8 studies and all 828 patients showed statistically significant results favoring the use of postoperative drainage concerning recurrence rates (RR 0.48, 95% CI 0.34–0.66, $P < 0.00001$) (Figure 1). A meta-analysis limited to the results of 3 studies with adequate allocation concealment[55,70,75] involving 384 participants also showed statistically significant results favoring the use of postoperative drainage (RR 0.38, 95% CI 0.22–0.65, $P = 0.0004$) (Figure 2). No statistically significant differences between the 2 interventions were found in the meta-analyses regarding mortality at final follow-up among 609 patients,[55,56,63,70,74,76] (Figure 3), complications other than recurrence and death among 672 patients,[55,56,63,65,70,74] (Figure 4), good recovery at final follow-up among 175 patients[55,56,63,76] (Figure 5), infections among 366 patients[56,65,74] (Figure 6),

Table 4. Details on Risks of Other Bias: Unevenness of the Preoperative modified Rankin Scale (mRS) Scores

Unclear risks	Santarius 2009[70]	This trial reported on 6 outcome analyses with adjusted logistic regression models by independent variables and their *P* values on its page 1072. The *P* values of the effects of the use of postoperative drain compared with the *P* values of the effects of the admission mRS[78] scores on these 6 outcomes, were: (1) for *recurrence rate*, 0.0210 versus 0.4770; (2) for *mortality at 30 days*, 0.2870 versus 0.0510; (3) for *mortality at 6 months*, 0.0330 versus 0.0070; (4) for *unfavorable mRS (4–6) at discharge*, 0.0330 versus <0.0001; (5) for *unfavorable mRS (4–6) at 6 months*, 0.2073 versus 0.0147; and (6) for *Glasgow Coma Scale score of 15 (full consciousness) at discharge*, 0.0334 versus 0.0002. These comparisons showed that the effect of the use of subdural drains, with direct local biomechanical effects on this space, was superior to the effect of admission mRS concerning the recurrence of subdural hematomas. However, the effect of admission mRS score, which reflects the preoperative clinical state, was greater than the effect of the use of drains concerning the 5 clinical outcomes analyzed. For each of the 5 clinical outcomes, the effect of admission mRS score was greater than the effect of the use of drain. These data showed a remarkable prognostic value of the mRS score at admission, a reliable measurement of the initial clinical state. On the other hand, according to the baseline characteristics shown on page 1068 of the trial report, among the 32 patients with admission mRS scores of 2 (slight disability), there were more patients randomized for drain than for no drain (21 vs. 11), whereas among the 56 patients with admission mRS score of 5 (severe disability), there were fewer patients randomized for drain than for no drain (23 vs. 33). mRS score of 5 (severe disability) is applied to patients who are bedridden, incontinent and requiring constant nursing care and attention. mRS score of 6 refers to death.[78] Compared with the group randomized to receive no drain, the group randomized to receive a drain had more patients with slight disability and fewer patients with severe disability. Regarding mRS scores of 1, 3, and 4, the preoperative distributions between the two groups were almost identical. The overall admission mRS data distribution, with all 5 scores analyzed together, was statistically homogeneous ($P = 0.20$). Nevertheless, considering the strong clinical prognostic effects of admission mRS score, it is likely that the unevenness of scores 2 and 5 favored the results of the drain group for all clinical outcomes, except recurrences. In fact, considering the adjustment for confounding factors, the trial authors stated on page 1071 that drain was not predictive of mRS score at 6 months and that admission mRS score was a significant predictor of this score at 6 months.
	Kaliaperumal 2012[64]	The trial authors comment that preoperative mRS scores were better in the subperiosteal drain group than in the subdural drain group, causing a potential bias in the overall outcome and subsequent results. Our analysis showed that the preoperative mean difference in mRS scores was slightly favorable to the subperiosteal drainage group, with no statistical significance ($P = 0.61$).

seizures among 296 patients[65,74] (Figure 7), or early Glasgow Coma Scale of 15 among 431 patients.[63,70,74] The analysis of the data from individual studies of outcomes that were not meta-analyzed did not show any other clear benefit or harms associated with the use of drains. As shown in the figures and in Table 5, the number of patients varied according to the primary studies involved in each outcome analysis.

Comparison 2. Treatment of CSDH with (A) 1 or 2 twist-drill craniostomies (with or without irrigation, and postoperative drainage to a suction reservoir or to a soft bag) versus (B) 1 or 2 burr-hole craniostomies, irrigation, and postoperative drainage to a soft bag. This comparison was performed by 4 studies: Gokmen et al.,[59] Gurelik et al.,[60] Muzii et al.,[66] and Singh et al.[73] No statistically significant differences between the treatments with twist-drill and burr-hole craniostomies were found in the meta-analyses of the data from these 4 studies regarding recurrence rates among 293 patients (Figure 8), mortality among 213 patients,[59,66,73] (Figure 9), other complications among 165 patients,[59,73] (Figure 10), or cure rates among 216 patients[59,66,73] (Figures 11 and 12).

Comparison 3. Treatment of CSDH in adults with 1 or 2 burr-hole craniostomies and postoperative bed header in (A) flat position versus (B) elevated position. This comparison was considered by 3 studies involving 189 patients: Abouzari et al.,[54] Ishfaq et al.,[62] and Nakajima et al.[68] No statistically significant differences between the 2 postoperative positions were found in the meta-analysis regarding recurrences among 189 patients[54,62,68] (Figure 13) and overall complications among 144 patients[54,62] (Figure 14). The data from Ishfaq et al.[62] from 60 patients showed that an elevated bed header position was associated with reduced length of hospital stay in days (mean difference 0.77, 95% CI 0.30–1.23, P = 0.001). No statistically significant differences were found regarding other outcomes.

Comparison 4. Treatment of unilateral CSDH in adults by 1 burr-hole craniostomy with irrigation and closed-system drainage for 48 hours with the subdural drainage catheter tip positioned in the frontal region versus (A) the occipital region, (B) the parietal region, or (C) the temporal base region. A trial was performed by Nakaguchi et al.[67] in 63 patients. No statistically significant differences were found between these procedures regarding recurrence rates, although there was a tendency to favor the frontal position.

Comparison 5. Treatment of CSDH with single burr-hole craniostomy and irrigation followed by postoperative subdural or subperiosteal drainage and daily treatment over 3 months with (A) perindopril versus (B) placebo. A trial was performed by Poulsen et al.[69] in 47 patients. There were no recurrences, surgical complications, or deaths. There were no statistically significant differences regarding medical complications or the volume of remnant CSDH 6 weeks postoperatively.

Comparison 6. Treatment of adults with high risk of recurrence of CSDH with 1 burr-hole craniostomy, closed drainage over 24 hours, and intravenous tranexamic acid over 24 hours, associated with intraoperative irrigation with (A) thrombin solution (100

Table 5. Effects of Interventions with Comments (15 Comparisons from 24 Studies)

First Author and Year	Outcomes	Risk Ratio RR or Mean Difference (95% CI)	*P* Values	I^2*
Comparison 1: Treatment of CSDH with burr-hole and irrigation of the subdural space associated with (A) postoperative closed drainage system to a soft bag versus (B) no postoperative drainage				
Ahmed 2011,[55] Erol 2005,[56] Javadi 2011,[63] Laumer 1989,[65] Santarius 2009,[70] Singh 2014,[74] Tsutsumi 1997,[75] Wakai 1990.[76] All studies that made the comparison. (N = 828)	Recurrences (n = 828), **Figure 1**	RR 0.48 (0.34–0.66)	< 0.00001	36%
Ahmed 2011,[55] Santarius 2009,[70] Tsutsumi 1997.[75] Only studies with adequate allocation concealment. (N = 384)	Recurrences (n = 384), **Figure 2**	RR 0.38 (0.22–0.65)	0.0004	1%
Ahmed 2011,[55] Erol 2005,[56] Javadi 2011,[63] Santarius 2009,[70] Singh 2014,[74] Wakai 1990[76] (N = 609)	Mortality at final follow-up (n = 609), **Figure 3**	RR 0.82 (0.49–1.37)	0.46	11%
Ahmed 2011,[55] Erol 2005,[56] Javadi 2011,[63] Laumer 1989,[65] Santarius 2009,[70] Singh, 2014[74] (N = 672)	Complications other than recurrence and death (n = 672), **Figure 4**	RR 0.96 (0.73–1.27)	0.77	32%
Ahmed 2011,[55] Erol 2005,[56] Javadi 2011,[63] Wakai 1990[76] (N = 175)	Good recovery at final follow-up (n = 175), **Figure 5**	RR 1.08 (0.90–1.28)	0.41	14%
	Results of Santarius et al.[70] not included because the use of drain was not predictive of mRS score at 6 months, whereas admission mRS score was a significant predictor of it (p. 1071 of the trial report).			
Erol 2005,[56] Laumer 1989,[65] Singh 2014[74] (N = 366)	Infections (n = 366), **Figure 6**	RR 0.82 (0.47–1.45)	0.50	0%
Laumer 1989,[65] Singh 2014[74] (N = 296)	Seizures (n = 296), **Figure 7**	RR 0.77 (0.30–2.01)	0.60	0%
Santarius 2009,[70] Javadi 2011,[63] Singh 2014[74] (N = 455)	Early GCS score of 15 (n = 431), random effects model	RR 1.10 (0.88–1.36)	0.40	54%
	Santarius et al.[70] found statistically significant benefit of early GCS score of 15 associated with the use of drains, but this outcome was subject to an unclear risk of bias, as seen in **Table 4**.			
Santarius 2009[70] (N = 215)	Mortality at 30 days (n = 211)	RR 0.50 (0.15–1.59)	0.24	
	Gross focal neurologic deficits at 6 months (n = 132)	RR 0.91 (0.43–1.96)	0.82	
	High level of care at 6 months (n = 134)	RR 0.56 (0.20– 1.57)	0.27	
	Worse mobility at 6 months (n = 102)	RR 0.57 (0.26– 1.24)	0.16	
Singh 2014[74] (N = 200)	Intracerebral hematoma (n = 200)	RR 1.33 (0.31–5.81)	0.70	
	Subdural empyema (n = 200)	RR 0.50 (0.09– 2.67)	0.42	
	Pneumocephalus with mass effect (n = 200)	RR 1.25 (0.35–4.52)	0.73	
	Residual hemiparesis (n = 200)	RR 0.58 (0.24–1.42)	0.24	
	Pulmonary embolism (n = 200)	RR 1.00 (0.06–15.77)	1.00	
Comment: In conclusion, postoperative closed drainage to a soft bag resulted in a statistically significant reduction of the recurrence rate with no other clear benefit or harm.				
Comparison 2: Treatment of CSDH with (A) 1 or 2 twist-drill craniostomies (with or without irrigation, and postoperative drainage to suction reservoir or to a soft bag) versus (B) 1 or 2 burr-holes craniostomies, irrigation and postoperative drainage to a soft bag				
Gokmen 2008,[59] Gurelik 2007,[60] Muzii 2005,[66] Singh 2011[73] (N = 311)	Recurrences (n = 293), **Figure 8**	RR 0.66 (0.31–1.40)	0.28	27%
Gokmen 2008,[59] Muzii 2005,[66] Singh 2011[73] (N = 231)	Mortality (n = 213), **Figure 9**	RR 2.02 (0.68–6.04)	0.21	13%
Gokmen 2008,[59] Singh 2011[73] (N = 170)	Complications other than recurrence and death (n = 165), **Figure 10**	RR 1.50 (0.62–3.61)	0.37	45%
Gokmen 2008,[59] Muzii 2005,[66] Singh 2011[73] (N = 231)	Cure (n = 216), fixed-effects model, **Figure 11**	RR 0.96 (0.86–1.08)	0.55	60%
Gokmen 2008,[59] Muzii 2005,[66] Singh 2011[73] (N = 231)	Cure (n = 216) random-effects model, **Figure 12**	RR 0.98 (0.80–1.21)	0.88	60%

Continues

Table 5. Continued

First Author and Year	Outcomes	Risk Ratio RR or Mean Difference (95% CI)	*P* Values	I^{2*}
Comment: Because of the substantial heterogeneity concerning cure rates, revealed by an I^2 greater than 50%, a random-effects Mantel-Haenszel model also was applied, resulting in wider confidence interval and a greater *P* value. No statistically significant differences found in the meta-analyses. These 4 trials presented differences among themselves regarding the surgical maneuvers associated with twist-drill craniostomies: irrigation or no irrigation, and passive or active drainage. Nevertheless, the individual analyses of the data of each of these trials resulted in no statistically significant differences between twist-drill craniostomies and burr-hole craniostomies regarding the aforementioned outcomes. Some authors advocated the use of twist-drill craniostomies because they are faster and can be performed at bedside under local anesthesia. Larger studies with lower risks of bias are necessary.				
Comparison 3: Treatment of CSDH in adults with 1 or 2 burr-hole craniostomies and postoperative bed header in (A) flat position versus (B) elevated position				
Abouzari 2007[54], Ishifaq 2009[62], Nakajima 2002[68] (N = 189)	Recurrences (n= 18 9), **Figure 13**	RR 1.07 (0.42–2.69)	0.89	0%
Abouzari 2007[54], Ishifaq 2009[62] (N = 144)	Overall complications (n = 144), **Figure 14**	RR 1.22 (0.73– 2.04)	0.44	0%
Ishifaq 2009[62] (N = 60)	Hospital stay (n = 60)	Mean difference 0.77 (0.30–1.23)	0.001	
	Wound infection (n = 60)	RR 2.00 (0.19–20.90)	0.56	
	Seizures (n = 60)	RR 0.67 (0.12– 3.71)	0.64	
Abouzari 2007[54] (N = 84)	Atelectasis (n = 84)	RR 1.43 (0.60–3.40)	0.42	
	Pneumonia (n = 84)	RR 1.25 (0.36–4.33)	0.73	
	Decubitus ulcer (n = 84)	RR 1.50 (0.26–8.52)	0.65	
	Deep-vein thrombosis (n = 84)	RR 0.33 (0.01– 7.96)	0.50	
Comment: No statistically significant differences found, except for reduction in the length of hospital stay found among 60 patients in one study.				
Comparison 4: Treatment of unilateral CSDH in adults by 1 burr-hole craniostomy with irrigation and closed-system drainage for 48 hours with the subdural drainage catheter tip positioned in the frontal region versus (A) the occipital region, (B) the parietal region, or (C) the temporal base region				
Nakaguchi 2000[67] (N = 63)	A) Frontal versus occipital (n = 46): recurrences	RR 0.24 (0.03–1.88)	0.17	
	B) Frontal versus parietal (n = 29): recurrences	RR 0.13 (0.02–1.05)	0.06	
	C) Frontal versus temporal base (n = 30): recurrences	RR 0.14 (0.02–1.20)	0.07	
Comment: It is believed that placing the catheter tip in the frontal region facilitates air removal, reducing the risks of recurrence. Statistical significance was not reached possibly due to the small sample sizes. Larger studies are necessary to evaluate this simple and possibly effective surgical measure better.				
Comparison 5: Treatment of CSDH with single burr-hole craniostomy and irrigation followed by postoperative subdural or subperiosteal drainage and daily treatment over 3 months with (A) perindopril versus (B) placebo				
Poulsen 2014[69] (N = 50)	No recurrences, surgical complications or deaths (n = 47)			
	Medical complications (dry coughs) (n = 47)	RR 4.42 (0.22– 87.44)	0.33	
	Preoperative CSDH volumes (mL) (n = 47)	Mean difference: –6.46 (–43.24, 30.32)	0.73	
	Volume of remnant CSDH 6 weeks postoperatively (mL) (n = 47)	Mean difference: –5.61 (–22.63, 11.41)	0.52	
Comment: No statistically significant differences were found. It is believed that angiotensin-converting enzyme inhibitors, such as perindopril, can reduce the development of new and immature blood vessels in the hematoma neomembrane, which could diminish the extravasation of fluid into the CSDH and reduce the risk of recurrence. Patients who were incapable of understanding and agreeing to participate were excluded from the study. Among the 50 randomized patients, 3 were excluded because they withdrew their consents, one from the perindopril and 2 from the placebo arm, and no further information about these patients was available.				
Comparison 6: Treatment of CSDH in adults with high risk of recurrence with 1 burr-hole craniostomy, closed drainage during 24 hours and intravenous tranexamic acid over 24 hours, associated with intraoperative irrigation with (A) thrombin solution (100 units/mL) versus (B) saline solution				
Shimamura 2009[71] (N = 79)	Recurrences (n = 79)	RR 0.22 (0.05–0.92)	0.04	

Continues

Table 5. Continued

First Author and Year	Outcomes	Risk Ratio RR or Mean Difference (95% CI)	*P* Values	I^2*
Comment: Tranexamic acid is an antifibrinolytic drug. The trial authors postulated that thrombin irrigation of the subdural space could induce a hemostatic reaction in the sinusoidal vessels situated in the CSDH capsule and avoid recurrences. The study involved adult patients with high risk of recurrence, including those with old age, use of antiplatelets, anticoagulants, hematologic disease, chronic renal failure, liver cirrhosis, and recurrence from previous drainage. The analysis showed that the intraoperative irrigation with thrombin solution was associated with a statistically significant lower recurrence rate. Further studies are recommendable. It would be interesting to examine the effectiveness of thrombin solution irrigation in CSDH patients commonly seen in practice, with the usual risks of recurrence.				
Comparison 7: Treatment of CSDH in adults with twist-drill craniostomy and no irrigation, followed by closed system drainage over (A) 48 hours versus (B) 96 hours				
Sindou 2010 and Ibrahim 2010[72] (N = 65)	General complication rate (n = 65)	RR 0.12 (0.02–0.94)	0.04	
	Neurologic complications (n = 65)	RR 0.86 (0.13–5.72)	0.87	
	Recurrences (n = 65)	RR 1.14 (0.28– 4.71)	0.85	
	Reoperation because clinical status did not improve and residual hematoma was of a significant volume (n = 65)	RR 1.71 (0.16–17.98)	0.65	
	Overall deaths (n = 65)	RR 0.21 (0.03–1.81)	0.16	
	Deaths from neurologic causes (n = 65)	RR 0.86 (0.06–13.12)	0.91	
	Deaths of general causes (n = 65)	RR 0.12 (0.01–2.29)	0.16	
Comment: The analyses showed a statistically significant lower rate of general complications with the 48 hours of drainage. No other statistically significant differences were found.				
Comparison 8: Treatment of CSDH with burr-hole craniostomy, irrigation, drainage for 1 to 4 days and postoperative (A) Trendelenburg position, hyperhydration, and hypoxic training versus (B) supine position, oxygen and fluid restriction				
Gai 2002[57] (N = 120)	Postoperative subdural fluid accumulation (n = 120)	RR 0.44 (0.14–1.37)	0.16	
Comment: No statistically significant differences were found. The trial authors gave as an example of "hypoxic training" the blow up of a balloon.				
Comparison 9: Treatment of CSDH in adults with (A) craniotomy versus (B) mannitol infusion				
Gjerris 1974[58] (N = 9)	Failure rates (n = 9)	RR 0.18 (0.01– 2.25)	0.18	
Comment: The failures occurred in the seven patients randomized to the mannitol arm. These patients had to switch to craniotomy and the authors considered it unjustifiable to continue the trial.				
Comparison 10: Treatment of unilateral CSDH in adults with burr-hole craniostomy and irrigation, followed postoperatively by (A) etizolam versus (B) no etizolam				
Hirashima 2002[61] (N = 48)	Drop outs (n = 48) (all drop outs occurred in the etizolam group)	RR 19.00 (1.17–309.11)	0.04	
	Recurrences (n = 36) (available cases analysis)	RR 0.17 (0.01– 2.92)	0.22	
	Volume of residual hematoma or dilated subdural space one month after surgery (n = 39) (available cases analysis)	Mean difference: −16.30 mL (−22.32, −10.28)	<0.00001	
Comment: According to the trial authors, etizolam is an antagonist of platelet-activating factor that could prevent CSDH recurrence. Nine patients were dropped from the study because the duration of etizolam administration was less than 3 days. The large losses in this arm of the study caused a very high risk of attrition bias.				
Comparison 11: Treatment of CSDH in adults with 2 burr-hole craniostomies and irrigation, followed over 48 hours postoperatively by (A) subperiosteal drainage to a minivac suction device versus (B) subdural drainage to a soft collection bag.				
Kaliaperumal 2012[64] (N = 52)	No recurrences (n = 50)			
	Deaths (n = 50)	RR 0.33 (0.01– 7.81)	0.49	
	Complications other than death (n = 50)	RR 1.00 (0.07, 15.12)	>0.99	
	Preoperative MRS (n = 50)	Mean difference: −0.20 (−0.97, 0.57)	0.61	
	mRS scores 3 months after surgery (n = 50)	Mean difference: −0.52 (−1.01, −0.03)	0.04	
	MRS 6 months postoperatively (n=50)	Mean difference: −0.68 (−1.20, −0.16)	0.01	

Continues

Table 5. Continued

First Author and Year	Outcomes	Risk Ratio RR or Mean Difference (95% CI)	*P* Values	I^2*
Comment: In the subperiosteal technique, the standard silicone ventriculostomy tube was placed in such a manner as to cover both burr holes. Although this trial suggested that subperiosteal drainage to a minivac suction device could result in better clinical results than the commonly used subdural drainage to a soft collection bag, further studies are necessary. Two patients, one from each arm, were excluded from the study because of premature removal of drains before the end of the 48-hour period.				
Comparison 12: Treatment of CSDH in adults with 1 burr-hole irrigation and (A) permanent subdural drain and subcutaneous Rickham reservoir for percutaneous drainage versus (B) temporary subdural closed drainage system				
Laumer 1989[65] (N = 97)	Recurrences (n = 97)	RR 0.94 (0.48–1.85)	0.86	
	Infections (n = 97)	RR 0.51 (0.05–5.45)	0.58	
	Postoperative seizures (n = 97)	RR 2.04 (0.19–21.78)	0.55	
Comment: No statistically significant differences were found.				
Comparison 13: Treatment of CSDH in adults with 1 burr-hole irrigation and (A) permanent subdural drain and subcutaneous Rickham reservoir for percutaneous drainage versus (C) no postoperative drainage system				
Laumer 1989[65] (N = 95)	Recurrences (n = 95)	RR 0.98 (0.49–1.96)	0.95	
	Infections (n = 95)	RR 0.98 (0.06– 15.20)	0.99	
	Postoperative seizures (n = 95)	RR 0.98 (0.14–6.67)	0.98	
Comment: No statistically significant differences were found. According to the report, new guidelines were established in their department following the trial: the permanent subdural drain connected to a Rickham reservoir for percutaneous drainage was indicated primarily in patients in whom the brain did not expand sufficiently during surgery and secondarily in those patients in whom reoperation became necessary. No other trials of this technique were found.				
Comparison 14: Treatment of CSDH in adults with 2 burr-hole craniostomies and postoperative 48–96 hours of drainage to a bag, associated with (A) continuous irrigation of the subdural space versus (B) no irrigation				
Ram 1993[52] (N = 37)	Recurrences (n = 37)	RR 0.24 (0.03–1.92)	0.18	
	Complications (n = 37)	RR 0.47 (0.10–2.28)	0.35	
Comment: No statistically significant differences were found. The objective of the continuous irrigation of the subdural space was to remove the fibrinolytic agents to avoid recurrences. Intracranial pressure was monitored via a strain gauge transducer connected to the irrigation drainage catheter to detect any possible malfunction of the draining catheters. One patient suffered transient deterioration of consciousness with hemiparesis as the result of blocked drains with a patent irrigation tube, but this complication was detected early and was reversed by replacement of the blocked drains. Continuous irrigation of the subdural space requires careful monitoring of the intracranial pressure in an intensive care unit.				
Comparison 15: Treatment of CSDH in adults with high risk of recurrence on antiplatelets, with 1 burr-hole craniostomy, closed drainage during 24 hours, and intravenous tranexamic acid over 24 hours, associated with intraoperative irrigation with (A) thrombin solution (100 units/mL) versus (B) saline solution				
Shimamura 2009[71] (N = 79)	Recurrences (n = 34) (available cases analysis)	RR 0.11 (0.01–1.91)	0.13	
Comment: This comparison, limited to 34 patients on antiplatelets, was done in a subgroup of the originally randomized study with 79 patients with high risk of recurrences of various causes. No statistically significant differences were found.				

RR, risk ratio; CI, confidence interval; I^2, inconsistency index; N, number of randomized patients; n, number of patients available for the outcome analysis; CSDH, chronic subdural hematoma; mRS, modified Rankin Scale; GCS, Glasgow Coma Scale.

The overlapping of CIs, which occur at variable degrees, can be seen in the figures showing the forest plots on the meta-analyses. A lack of overlap of CIs means strong statistical heterogeneity.

*A rough guide to interpretation of the heterogeneity according to the I^2 is as follows: 0%–40%, might not be important; 30%–60%, may represent moderate heterogeneity; 50%–90%, may represent substantial heterogeneity; 75%–100%, considerable heterogeneity.[51]

unit/mL) versus (B) saline solution. A trial was performed by Shimamura et al.[71] in 79 patients. Irrigation with thrombin solution resulted in a statistically significant reduction in the rate of recurrences (RR 0.22, 95% CI 0.05–0.92, P = 0.04).

Comparison 7. Treatment of CSDH in adults with twist-drill craniostomy and no irrigation, followed by closed system drainage during (A) 48 hours versus (B) 96 hours. Trials were performed in 65 patients and reported by Sindou et al.[72] and Ibrahim et al.[77] The shorter drainage duration was associated with statistically significant lower rates of general complication (RR 0.12, 95% CI 0.02–0.94, P = 0.04). No statistically significant differences were found regarding other outcomes.

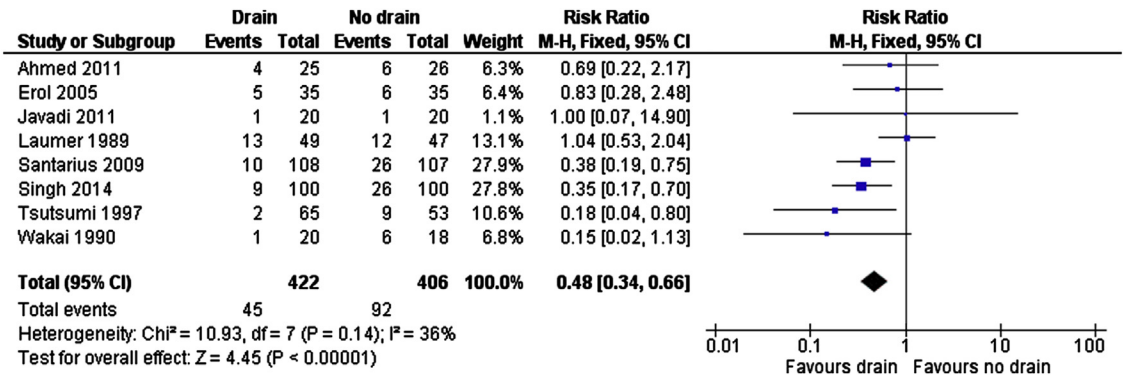

Figure 1. Forest plot showing the effects of treatment of chronic subdural hematomas with burr-hole craniostomy and irrigation of the subdural space associated with (A) a postoperative closed drainage system to a soft bag versus (B) no postoperative drainage. Outcome: *Recurrences requiring reoperation* (all studies). CI, confidence interval.

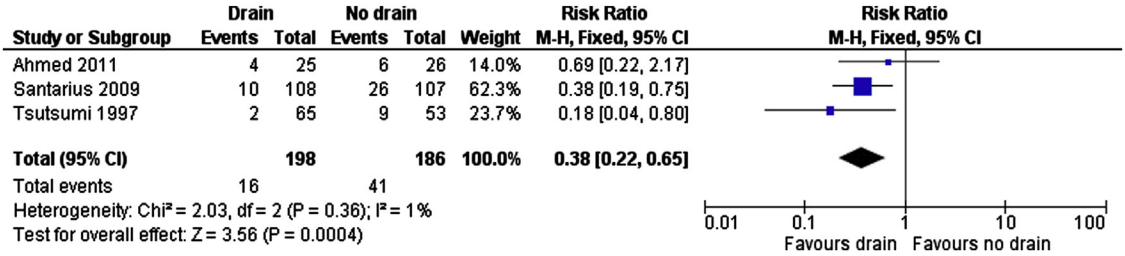

Figure 2. Treatment of chronic subdural hematomas with burr-hole craniostomy and irrigation of the subdural space associated with (A) a postoperative closed drainage system to a soft bag versus (B) no postoperative drainage. Outcome: *Recurrences requiring reoperation* (only studies with adequate allocation concealment).

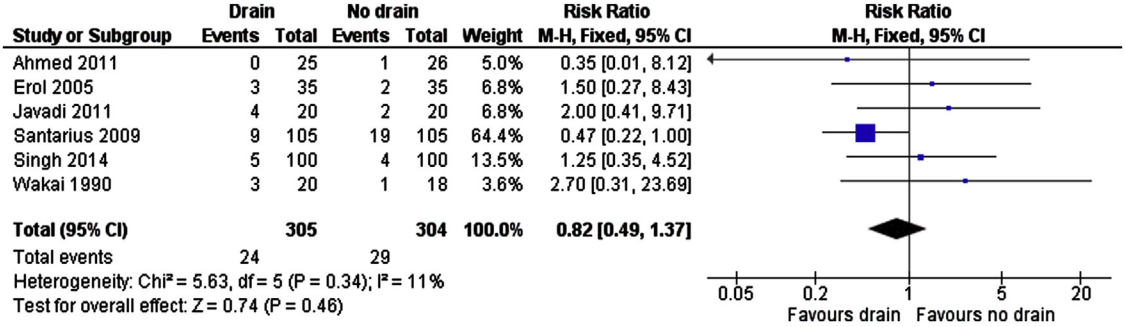

Figure 3. Treatment of chronic subdural hematomas with burr-hole craniostomy and irrigation of the subdural space associated with (A) a postoperative closed drainage system to a soft bag versus (B) no postoperative drainage. Outcome: *Mortality rates at final follow-up.*

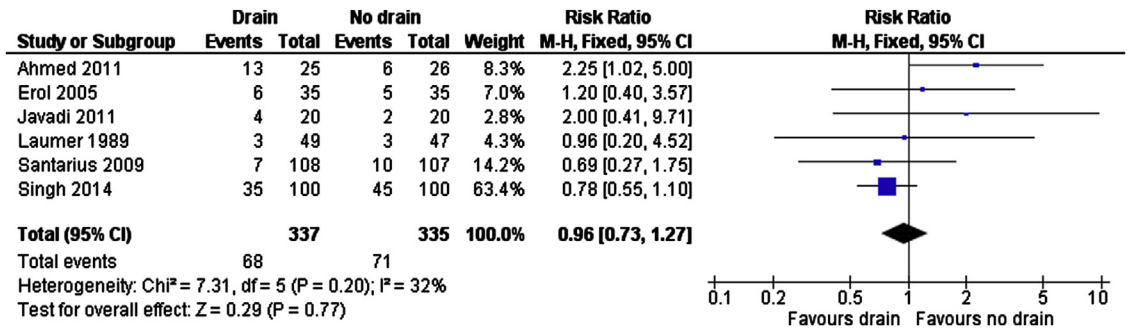

Figure 4. Treatment of chronic subdural hematomas with burr-hole craniostomy and irrigation of the subdural space associated with (A) a postoperative closed drainage system to a soft bag versus (B) no postoperative drainage. Outcome: *Complications other than recurrence and death*.

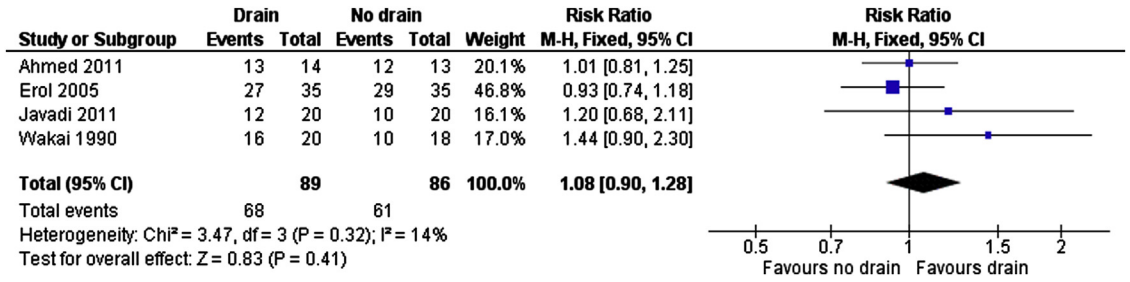

Figure 5. Treatment of chronic subdural hematomas with burr-hole craniostomy and irrigation of the subdural space associated with (A) a postoperative closed drainage system to a soft bag versus (B) no postoperative drainage. Outcome: *Good recovery at final follow-up*.

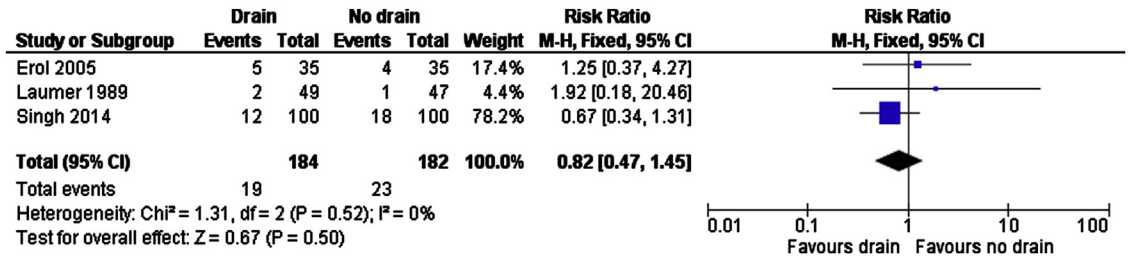

Figure 6. Treatment of chronic subdural hematomas with burr-hole craniostomy and irrigation of the subdural space associated with (A) a postoperative closed drainage system to a soft bag versus (B) no postoperative drainage. Outcome: *Infections*.

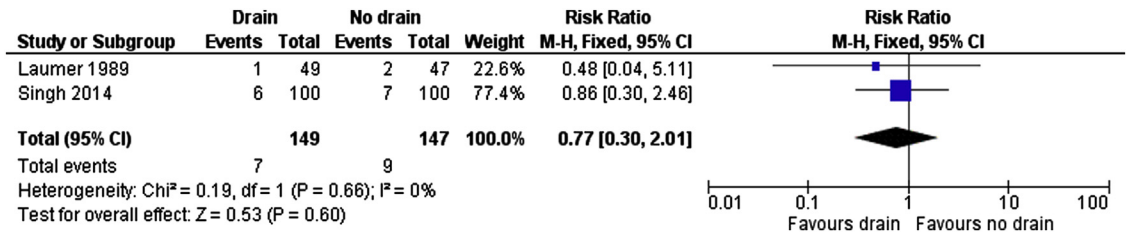

Figure 7. Treatment of chronic subdural hematomas with burr-hole craniostomy and irrigation of the subdural space associated with (A) a postoperative closed drainage system to a soft bag versus (B) no postoperative drainage. Outcome: *Seizures*.

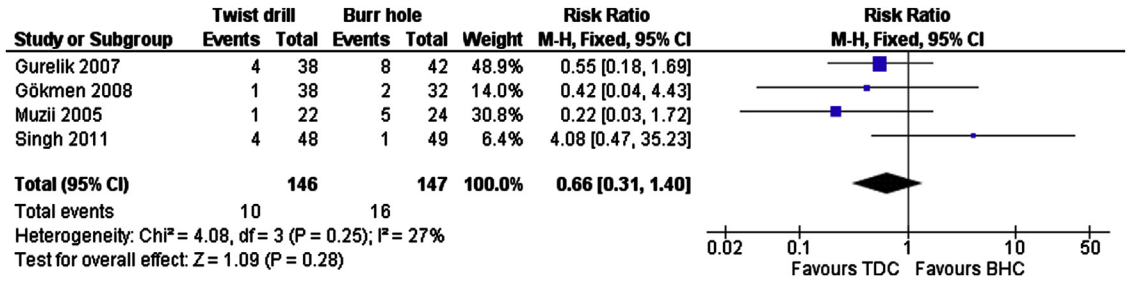

Figure 8. Treatment of chronic subdural hematomas with (A) 1 or 2 twist-drill craniostomies (TDC), with or without irrigation, and postoperative drainage to a suction reservoir or to a soft bag, versus (B) 1 or 2 burr-hole craniostomies (BHC), irrigation, and postoperative drainage to a soft bag. Outcome: *Recurrences requiring reoperation*.

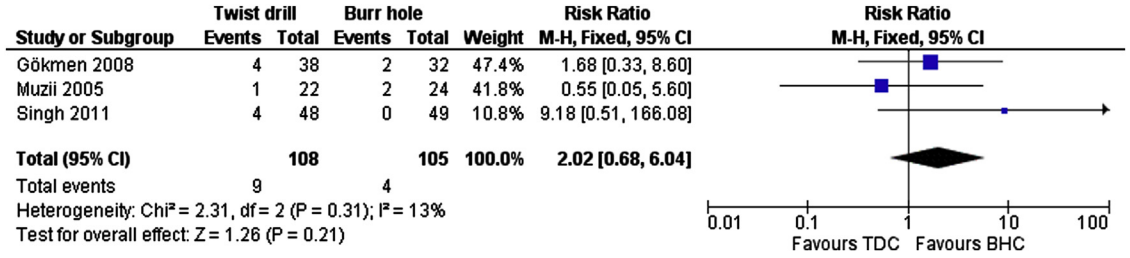

Figure 9. Treatment of chronic subdural hematomas with (A) 1 or 2 twist-drill craniostomies (TDC), with or without irrigation, and postoperative drainage to a suction reservoir or to a soft bag, versus (B) 1 or 2 burr-hole craniostomies (BHC), irrigation, and postoperative drainage to a soft bag. Outcome: *Mortality rates*.

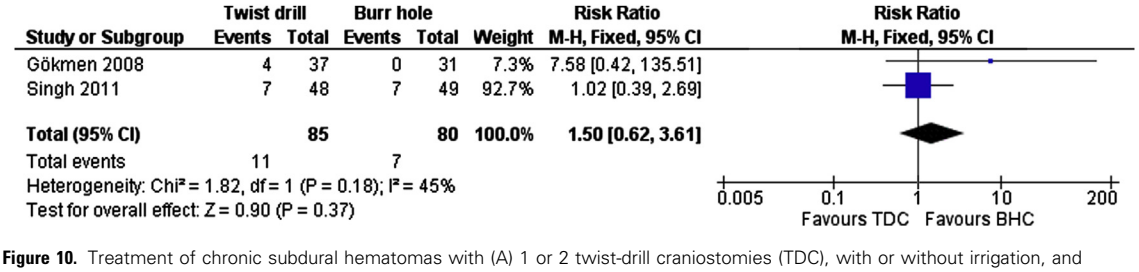

Figure 10. Treatment of chronic subdural hematomas with (A) 1 or 2 twist-drill craniostomies (TDC), with or without irrigation, and postoperative drainage to a suction reservoir or to a soft bag, versus (B) 1 or 2 burr-hole craniostomies (BHC), irrigation, and postoperative drainage to a soft bag. Outcome: *Complications other than recurrences and deaths*.

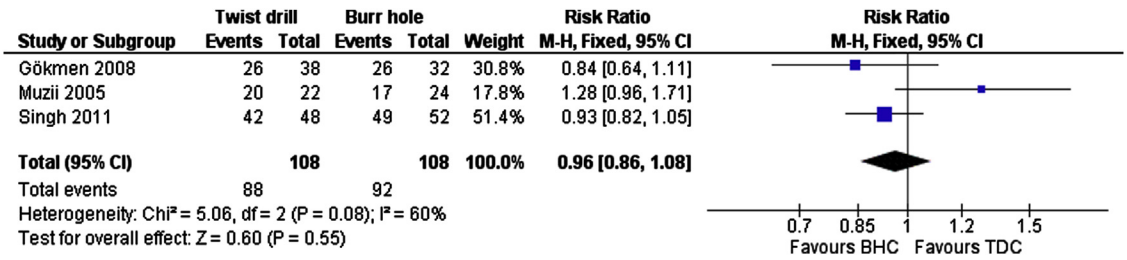

Figure 11. Treatment of chronic subdural hematomas with (A) 1 or 2 twist-drill craniostomies (TDC; with or without irrigation, and postoperative drainage to a suction reservoir or to a soft bag) versus (B) 1 or 2 burr-hole craniostomies (BHC), irrigation, and postoperative drainage to a soft bag. Outcome: *Cure (fixed effects model)*.

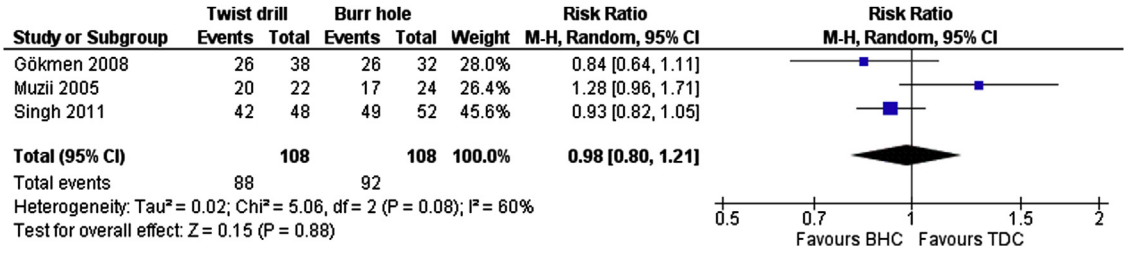

Figure 12. Treatment of chronic subdural hematomas with (A) 1 or 2 twist-drill craniostomies (TDC; with or without irrigation, and postoperative drainage to a suction reservoir or to a soft bag) versus (B) 1 or 2 burr-hole craniostomies (BHC), irrigation, and postoperative drainage to a soft bag. Outcome: *Cure (random effects model)*.

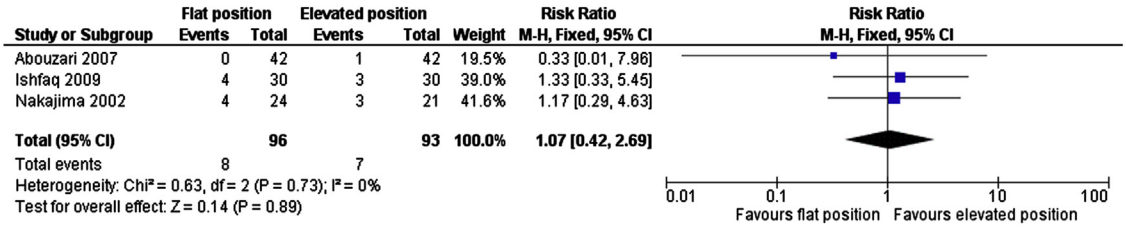

Figure 13. Treatment of chronic subdural hematomas in adults with burr-hole craniostomies and postoperative bed header in (A) flat position versus (B) elevated position. Outcome: *Recurrences requiring reoperation*.

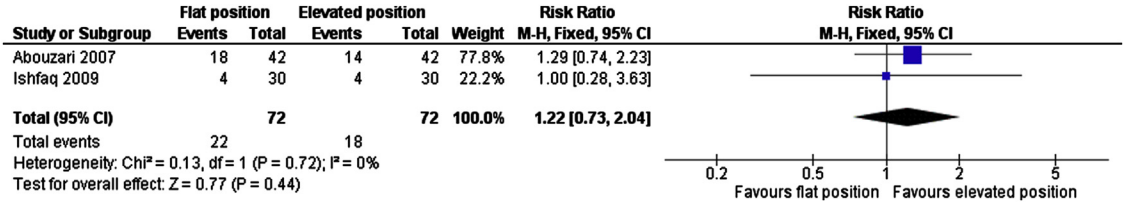

Figure 14. Treatment of chronic subdural hematomas in adults with burr-hole craniostomies and postoperative bed header in (A) flat position versus (B) elevated position. Outcome: *Overall complications*.

Table 6. Summary of Main Findings and Quality of Evidence

Comparison 1: Treatment of CSDH with burr hole and irrigation of the subdural space associated with (A) postoperative closed drainage system to a soft bag versus (B) no postoperative drainage

Outcome	Drain	No Drain	Relative Effect (95% CI)	Number of patients	Quality of evidence (GRADE)	Comments
Recurrence	16/198 (8.1%)	41/186 (22.0%)	RR 0.38 (0.22–0.65)	384 (only the 3 studies with adequate allocation concealment)	Moderate to high	$I^2 = 1\%$, NNT = 8
Mortality at final follow-up	24/305 (7.9%)	29/304 (9.5%)	RR 0.82 (0.49–1.37)	609 (6 studies)	Moderate	$I^2 = 11\%$
Complications other than recurrences and deaths	68/337 (20.2%)	71/335 (21.2%)	RR 0.96 (0.73–1.27)	672 (6 studies)	Moderate	$I^2 = 32\%$
Good recovery at final follow-up	68/89 (76.4%)	61/86 (70.9%)	RR 1.08 (0.90–1.28)	175 (4 studies)	Moderate	$I^2 = 14\%$
Infections	19/184 (10.3%)	23/182 (12.6%)	RR 0.82 (0.47–1.45)	366 (3 studies)	Moderate	$I^2 = 0\%$
Seizures	7/149 (4.7%)	9/147 (6.1%)	RR 0.77 (0.30– 2.01)	296 (2 studies)	Moderate	$I^2 = 0\%$
Early postoperative GCS score of 15	148/214 (69%)	137/217 (63%)	RR 1.10 (0.88– 1.36)	431 (3 studies)	Moderate	$I^2 = 54\%$,

Comparison 2: Treatment of CSDH with (A) 1 or 2 twist-drill craniostomies (with or without irrigation, and postoperative drainage to a suction reservoir or to a soft bag) versus (B) 1 or 2 burr-hole craniostomies, irrigation and postoperative drainage to a soft bag

Outcome	Twist Drill	Burr Hole	Relative Effect (95% CI)	Number of Patients (Studies)	Quality of Evidence (GRADE)	Comments
Recurrences	10/146 (6.8%)	16/147 (10.9%)	RR 0.66 (0.31– 1.40)	293 (3 studies)	Low	$I^2 = 27\%$
Mortality	9/108 (8.3%)	4/105 (3.8%)	RR 2.02 (0.68–6.04)	213 (3 studies)	Low	$I^2 = 13\%$
Complications other than recurrences and deaths	11/85 (12.9%)	7/80 (8.7%)	RR 1.50 (0.02–3.61)	165 (2 studies)	Low	$I^2 = 45\%$
Cure	88/108 (81.5%)	92/108 (85.2%)	RR 0.98 (0.80–1.21)	216 (3 studies)	Low	$I^2 = 60\%$

Comparison 3: Treatment of CSDH in adults with 1 or 2 burr-hole craniostomies and postoperative bed header in (A) flat position versus (B) elevated position

Outcome	Flat Position	Elevated Position	Relative Effect (95% CI)	Number of Patients (Studies)	Quality of Evidence (GRADE)	Comments
Recurrences	8/96 (8.3%)	7/93 (7.5%)	RR 1.07 (0.42–2.69)	189 (3 studies)	Low	$I^2 = 0\%$
Overall complications	22/72 (30.6%)	18/72 (25%)	RR 1.22 (0.73– 2.04)	144 (2 studies)	Low	$I^2 = 0\%$

Comparison 4: Treatment of unilateral CSDH in adults by 1 burr-hole craniostomy with irrigation and closed-system drainage for 48 hours with the subdural drainage catheter tip positioned in the frontal region versus the occipital region.

Outcome	Frontal Region	Occipital Region	Relative Effect (95% CI)	Number of Patients (Studies)	Quality of Evidence (GRADE)	Comments
Recurrence	1/21 (5%)	5/25 (20%)	RR 0.24 (0.03, 1.88)	46 (1 study)	Low	

Comparison 5: Treatment of CSDH with single burr-hole craniostomy and irrigation followed by postoperative subdural or subperiosteal drainage and daily treatment during 3 months with (A) perindopril versus (B) placebo

Outcome	Perindopril (ACE inhibitor)	Placebo	Relative Effect (95% CI)	Number of Patients (Studies)	Quality of the Evidence (GRADE)	Comments
Volume of remnant CSDH 6 weeks postoperatively (mL)	22.77 (SD 31.3) n = 25	28.3 (SD 28.24) n = 22	Mean difference −5.61 (−22.63, 11.41)	47 (1 study)	Moderate	No recurrences; the trial excluded patients with impaired consciousness.

Continues

Table 6. Continued

Comparison 6: Treatment of adults with high-risk of recurrence CSDH with 1 burr-hole craniostomy, closed drainage during 24 hours, and intravenous tranexamic acid during 24 hours, associated with intraoperative irrigation with (A) thrombin solution (100 unit/mL) versus (B) saline solution

Outcome	Thrombin Solution	Saline Solution	Relative Effect (95% CI)	Number of Patients (Studies)	Quality of Evidence (GRADE)	Comments
Recurrences	2/36 (5.6%)	11/43 (25.6%)	RR 0.22 (0.05–0.92)	79 (1 study)	Moderate	NNT= 5

Comparison 7: Treatment of CSDH in adults with twist-drill craniostomy and no irrigation, followed by closed system drainage during (A) 48 hours versus (B) 96 hours

Outcome	48 Hours	96 Hours	Relative Effect (95% CI)	Number of Patients (Studies)	Quality of Evidence (GRADE)	Comments
General complications	1/35 (2.9%)	7/30 (23.3%)	RR 0.12 (0.02–0.94)	65 (1 study)	Moderate	NNT= 5

CSDH, chronic subdural hematoma; RR, risk ratio; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; I^2, inconsistency index; NNT, number needed to treat; GCS, Glasgow Coma Scale; ACE, angiotensin-converting enzyme.

GRADE Working Group grades of evidence. *High quality:* Further research is very unlikely to change our confidence in the estimate of effect. *Moderate quality:* Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. *Low quality:* Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. *Very low quality:* An estimate of effect is very uncertain.

Comparisons 8–15. Comparisons 8–15 are shown in Table 5.

DISCUSSION

We will discuss only the main findings. For a summary, including the quality of the evidence (Grading of Recommendations Assessment, Development and Evaluation Working Group), see Table 6. The use of postoperative drains after burr-hole evacuation of CSDH reduced the rate of recurrences by a statistically significant level, with no other clear benefits or harms. The postoperative drainage time lasted approximately 2 days. The use of drains is a common procedure used in various surgical fields to eliminate blood or secretions, and it would be expected to reduce the rate of recurrences of CSDHs through its local biomechanical effects. Although the rate of recurrence was reduced, no significant clinical benefits were found associated with this reduction. Clinical benefits from burr-hole craniostomies seemed to be more dependent on the patient's preoperative clinical state than on the use of drains, as indicated by the data of a regression logistic analysis,[70] discussed in Table 4. Regarding common concerns with the use of drains because of the potential risks of infections, cortical injuries, and seizures, no statistically significant side effects were identified.

The treatment of CSDH with twist drills compared with burr-hole craniostomies showed no significant differences regarding recurrence, mortality, other complications, or cure rates based on studies with mostly unclear or high risks of bias. Several authors have advocated the use of twist-drill craniostomies because they are faster and can be performed at bedside under local anesthesia. Larger studies with a lower risk of bias are needed.

The treatment of adults with 1 or 2 burr-hole craniostomies and postoperative bed headers in flat versus elevated positions, according to the data from primary studies with mostly unclear risks of bias, showed no statistically significant differences regarding recurrences or other complications. One study[62] showed a significant reduction in the length of hospital stay associated with elevated positioning.

The treatment of CSDH by one burr-hole craniostomy with irrigation and closed system drainage with the subdural catheter tip positioned in the frontal region instead of other regions resulted in reductions in the recurrence rates that did not reach statistical significance in a small study[67] with mostly unclear risks of bias. Larger studies could better evaluate this simple and possibly helpful procedure.

After evacuation of CSDH, the postoperative administration of perindopril, compared with placebo, did not result in a significant reduction in the volume of the remnant CSDH.[69] No recurrence occurred in either group. It is believed that angiotensin-converting enzyme inhibitors, such as perindopril, can reduce the development of new and immature blood vessels in the hematoma neomembrane, which would diminish the extravasation of fluid into the CSDH and reduce the risk of recurrence.

The treatment of adults with high risk of recurrence of CSDH with burr-hole craniostomy, closed drainage, and intravenous tranexamic acid associated with intraoperative irrigation with thrombin solution instead of irrigation with saline solution resulted in a statistically significant reduction in the rate of recurrence in a study[71] with low risks of bias in 79 patients. Tranexamic acid is an antifibrinolytic drug. The study involved older patients, use of antiplatelets or anticoagulants, hematologic disease, chronic renal failure, liver cirrhosis, and recurrence from previous drainage. Further studies are recommendable, and it would be interesting to evaluate the effectiveness of thrombin solution irrigation in patients with CSDH commonly seen in practice and presenting the usual risks of recurrence.

The treatment of CSDH with twist-drill craniostomy and no irrigation, followed by closed system drainage over 48 hours, instead of 96 hours, resulted in statistically significant lower general (non-neurological) complication rates in a study[72,77] with a mostly low risk of bias in 65 patients. No statistically significant differences were found regarding other outcomes.

The other 8 comparisons are commented on, along with the effects of their interventions, in Table 5. Most of the comparisons analyzed in this review

presented no statistically significant differences, and many studies were small or were associated with unclear or high risks of bias.

Main Aspects of This Review

Our broad search for RCTs of surgical treatments for CSDHs was unrestricted by language or publication date. The quantitative analyses, performed with the Cochrane statistical software, were independent of the analyses presented by the original trial reports.

Different from the other reviews of CSDHs, this review included unpublished data supplied by trial authors to eliminate doubts, quantitative analyses of all outcomes of practical interest found in each study, and a detailed critical analysis of the risks of bias, according to the Cochrane methods. Isolated studies were analyzed because this review was not restricted to meta-analyses, the statistical combination of results from two or more separate studies.

Instead of publishing various shorter reviews, all 15 comparisons contained in the 24 RCTs were presented in this single, comprehensive, critical, quantitative systematic review. This approach was used for the benefit of readers involved in busy neurosurgical practices or residence training.

Previous Reviews

Some reviews were not focused on RCTs. They analyzed Class II and Class III evidence[46]; used Monte Carlo simulation and sensitivity analyses,[49] combined prospective and retrospective studies[79]; reviewed retrospective studies[80]; or commented on various management issues in a narrative review.[81]

Four systematic reviews published in 2014 focused on RCTs, but they were mostly[82] or entirely[83-85] restricted to meta-analyses, and various outcomes of practical interest reported in the primary studies were not analyzed.

One of these reviews[85] covered medical and surgical therapies for CSDH based on 234 observational studies and 16 RCTs, applied language restrictions and classified all RCTs as presenting a low risk of performance bias despite the impossibility of blinding personnel and patients to most surgical procedures. Its meta-analyses of mortality considered one RCT data[59] before hospital discharge instead of overall deaths, and their data from another trial[73] differed from the trial report. Its meta-analyses lacked 2 older RCTs[55,76] and a new one.[74]

Two meta-analyses of another review[82] include 3 studies[86-88] that we did not classify as RCTs: one study[86] reported that the surgical procedure was up to the preference of the attending neurosurgeon on call; another[87] stated that their study was retrospective; and the other[88] reported that the operative techniques were randomized to the attending neurosurgeon, and because there were only 2 teams, they were randomized to either team A or team B, which were on call that day. This review[82] evaluated all of their included studies as presenting low risks for performance, detection, and reporting bias, unlike the usual views.[51] Its meta-analyses lacked one older RCT[62] and a new RCT.[74]

Two other reviews[83,84] evaluated studies with the commonly used Jadad scale, which emphasizes reporting rather than conduct and does not consider allocation concealment,[51] which is an essential aspect in the assessment of RCTs. The meta-analyses[83] of postoperative bed header position in CSDH included a study[89] that contains subacute hematomas.

One of these reviews[84] found a statistically significant reduction in the risk of poor functional outcome with the use of postoperative subdural drains. This undue positive finding was caused by the inclusion in their meta-analysis of the data of a study on the mRS score at 6 months, which suffered from confounding factors, as described in our **Table 4** ("Details on other bias").

Aside from the differences mentioned above, our results were similar to those obtained by these reviewers.[82-85]

Limitations of This Review

As shown in **Table 2**, regarding the risks of bias for each primary study, indicating an estimate of the extent to which the results can be trusted, most trials suffered from unclear or high risks, which weakened the strength of the evidences. Only 6 primary studies reported adequate allocation concealment with low risks of selection bias, whereas the concealment was unclear in 12 and inadequate in 6. Most of the outcome comparisons were restricted to small numbers of patients, and no multicentric studies were found. These limitations precluded strong and definitive conclusions.

This unfavorable scenario is common in all clinical areas, particularly in surgery, in which RCTs with a low risk of bias are more difficult to achieve. In contrast, it is encouraging that the still small number of RCTs is increasing steadily and more than half of the studies found for the present review were published in the last 10 years.

CONCLUSIONS

This comprehensive and best evidence-based quantitative systematic review indicated that the use of closed-system drainage after burr-hole evacuation reduced the rate of recurrences and was associated with no other significant benefit or harm, according to the data currently available. It also suggested that: (1) treatment with twist drills is equivalent to burr holes; (2) after burr-hole craniostomy, the postoperative bed header in the elevated position, instead of the supine position, might reduce the length of hospital stay; (3) irrigation of the subdural space with thrombin solution associated with postoperative tranexamic acid in patients with high risk of recurrence might reduce this risk; and (4) treatment with a twist drill, followed by closed-system drainage during 48 hours instead of 96 hours, might reduce general complication rates. Most trials available suffered from unclear or high risks of bias and involved small numbers of patients, precluding strong and definitive conclusions.

Implications for Clinical Research

CSDHs are common neurosurgical conditions and a rich field for basic and clinical investigations. We hope that this review, being critical and comprehensive and providing various comparisons that require further study of surgical treatments, might be useful to potential authors interested in preparing a RCT. It should help to avoid the commonly observed risks of bias, such as the use of alternation to allocate patients. Well-designed and -performed RCTs with low risks of bias are necessary for precise assessments of the effectiveness and safety of treatments. In a pragmatic trial addressing the effectiveness

of a treatment in real life, an intention-to-treat strategy should be adopted, maintaining the participants in the groups to which they were randomized regardless of withdrawals, noncompliance, or protocol deviations, thereby preserving the prognostic balance from the original random allocation, minimizing false-positive results, and favoring generalization. The protocol should include measures to avoid losses and, if possible, to follow up the patients who leave the study to obtain complete outcome data for every randomized participant. Attrition causes difficulties in the analyses of results, particularly when the event risks are low. Multicentric studies should be encouraged.[51,53,90-96]

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The research protocol was registered and approved by the Committee of Ethics in Research of the Federal University of Sao Paulo, on April 1, 2011, under the number CEP 0354/11.

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